

**A comprehensive Review on pandemic virus COVID-19 with reference to
Prognosis, Diagnosis & Therapeutics**

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Abstract

In last week of December 2019, WHO was informed about unidentified cases of pneumonia in Wuhan, Hubei Province, People's Republic of China. The symptoms were similar to viral pneumonia and after diagnosis and identification by Chinese Health authorities in first week of January 2020, [1] Coronavirus was identified as causative virus particle and named as novel coronavirus pneumonia. In last week of January 2020 following the recommendations of the emergency committee, The World Health Organization (WHO) declared the outbreak constitutes a public health emergency of international concern (PHEIC) [2]. The name 'CoVID-19' is given by World Health Organization (WHO) and Sever Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses (ICTV). The current level of knowledge on CoVID-19, world scientists gathered in February 2020 and discussed the critical research problems related to this curtail viral outbreak, to fight back for the current situation and the future as well. But still the exponential graph of this viral disease is growing higher and higher each day [3] [4].

It is highly contagious, circulates in nature due to spillover with a range of factors such as having several natural, intermediate and final host. The reservoir for CoVID-19 is not known yet but the genomic analysis had shown the similarity index is 76% and 96% between CoVID-19 and SARS-CoV-RaTG13 found in bats respectively. So it concluded that it might originated from bats. [5] [6]

Key Words: CoVID-19, SARS-CoV-2, Coronavirus, SARS, Sanatization, WHO.

Introduction

Coronavirus is a large group of enveloped RNA viruses, spherical or pleomorphic in shape. It carries petal like or club shaped peplomers on their surface. The name ‘corona’ refers to the fringe of surface projections which surrounds the virus which gives it resembles to the ‘solar corona’. They are divided into two groups of **acid labile viruses** (common cold) and acid stable viruses (gastroenteritis). There are many serotypes which are hard to diagnose, detect or culture. The first isolated virus of this family was from common cold case. It is the second most prominent causative agent of common cold cases after Rhinoviruses. [7]

Characteristics and Classification

Coronavirus is an enveloped virus which is spherical in shape. The particle size ranges from 120-160 nm in diameter with helical nucleocapsid which is of 9-11 nm in diameter. It consist of linear, non-segmented, positive sense of 27-32 kb single stranded RNA which is capped and polyadenylate. It is infectious in nature and one of the largest genome among viruses. Projections are of 20nm long which are widely spread. The viral structural proteins include phosphorylated nucleocapsid proteins, membrane protein or glycoproteins proteins that behaves as a matrix proteins which are embedded in the nucleocapsid, and the spikes glycoproteins that makeup the petal shaped peplomers. [7] [8] [9]

It causes common cold as well as SARS (Sever Acute Respiratory Syndrome Coronavirus). It have very high frequency of recombination. All the genres of coronaviruses affect animals, birds and humans. It displays very high frequency of recombination. It is hard to grow in cell cultures. Human infection is uncommon except few who adapted to human conditions. [8]

There are six recognized viruses from corona family that are known to cause human infections; Most of them belongs to Betacorona family except first two mentioned below:

1. Human Corona-229E;
2. Human Corona-NL63;
3. Human Corona-OC43;
4. Human Corona-HKU1;
5. SARS-CoV (Severe Acute Respiratory Syndrome);
5. MERS-CoV (Middle East Respiratory Syndrome);
6. COVID-19.

Some Human Corona Viruses (HCV) like OC43 contains third glycoprotein that causes hemagglutination & has acetyl esterase activity. The novel Coroavirus discovered in 2003 from patients of SARS is in the same group as OC43. [7] [8]

CLASSIFICATION	
FAMILY	CORONAVIRIDAE
ORDER	NIDOVIRINAE
SUB-FAMILIES	CORONAVIRINAE
	TOROVIRINAE
GENERA	ALPHA CORONA
	BETA CORONA
	GAMA CORONA
	DELTA CORONA

Replication of the virus particle:

A virus particle can only replicate in a living cell so it needs a host which can provide energy and a synthetic machinery (cell organelles) having all required precursors for the expression of viral genome to synthesize viral proteins. The nucleic acid of virus particle carries the 'genetic specificity' to code for all the specific and required macromolecules in an organized manner. The unique feature of viral replication is its interaction with the host cell receptors as the envelope proteins of the virus particle are similar to the host cell protein, after the viral particle gets adsorbed and entered the host cell, it gets disrupted losing its measurable infectivity, this phase of growth cycle is called the eclipse period. After a definite interval of eclipse period rapid accumulation of infectious progeny of virus particle takes place. [7]

Replication of some viruses is not very easy to study as they are hard to culture in laboratory, but some of them can be studied on cell cultures. Human corona virus do not grow well in cell cultures so the details have come from different studies of other viruses which are closely related to this virus particle. [8]

The replication cycle of coronavirus includes distinct ten steps including entry, replication of virus, latency, and shedding. The ten stages of the whole replication process is given below:

1. Reception at host receptors.
2. Entry and uncoating.
3. Endosome formation.
4. Release of genome.

5. Translation
6. Proteolysis
7. Replication
8. Transcription
9. Translation
10. Assembling of virus particle and release. [7]

The replication cycle of coronavirus takes place in cytoplasm. Virus targets the receptors of the host target cells and gets attached on their surface with the spikes (S) or hemagglutinin (HE) and binds to ACE-2. The receptor for human corona virus in human body cells is said to be the aminopeptidase N, and for SARS virus its angiotensin converting enzymes (ACE-2). The virus particle is then internalized by a mechanism known as absorptive endocytosis. The spike protein and HE protein may be responsible for the fusion of the viral envelope and the cell membrane/transmembrane (Serine protease, TMPRSS2) of the host. The very first step just after uncoating is the translation of polyproteins that encodes for replicase-transcriptase complex to produce a virus specific RNA dependent RNA polymerase. A full length complementary (minus strand) RNA is transcribed by the polymerase enzyme of the virus that serves as a template strand for a nested set of five to seven sub-genomic mRNA. The 5' terminal gene sequence of each mRNA gets translated. The full length genomic RNA copies gets transcribed and each sub-genomic mRNA is translated into a single polypeptide. In corona virus infection polyprotein precursors are not common, although a large polyprotein that get processed to yield the viral RNA polymerase is encoded by the genomic RNA. Neonate genomic RNA molecules interacts with the nucleocapsid protein in cytoplasm of host cell to form helical nucleocapsids. The leader RNA have a preferred binding site for N protein. The rough endoplasmic reticulum and Golgi bodies in areas containing viral glycoproteins releases nucleocapsids buds. After maturation the virions may transported to the periphery of the host cell in the form of vesicles for exit or release. Virions formed in corona infection are apparently not formed by budding through the plasma membrane. In some coronaviruses induced cell fusion is mediated by S protein. Some of the coronaviruses establish persistent infection rather being cytoidal. [10] [11] Coronavirus generally have a very high tendency of mutation during each round of replication, including the generation of substitution mutations and a high incidence of

deletion mutations which is a big threat for future. This virus undergoes high frequency of recombination which is very unusual for an RNA virus with a non-segmented genome and most of the time contributes to the evolution of a new virus strain like CoVID-19. [11]

Pathogenesis and Clinical features:

Coronavirus infections in humans usually remain limited to the upper respiratory tract but if severity increases can reach up to renal level. In contrast to SARS outbreak in 2003 was characterized by Serious respiratory illness including pneumonia, dyspnea and progression respiratory failure. Virus can also be detected in several organs, including liver, kidney, small intestine, and stool as well. Generally viruses of this family originates in non-human host mostly in bats, Chinese horseshoes bats are natural reservoir of corona like viruses due to widespread use of wild species for food and traditional medicines promotes the emergence of new viral strains. [7] [11] [12]

According to a retrospective study on clinical course an article published in 'The Lancet', after the completion of incubation period of 14-27 days symptoms may arise or may not be noticeable and within 3 days just after onset of infection the virus pass through the mucosal membranes of nasal passage and larynx, entering the lungs generating initial symptoms like fever, soreness in throat and cough occurs. After 4 to 9 days virus started to spread through lungs which results in breathing problems such as heavy breath, shortness of breath leading to hypoxia and acute respiratory distres. The virus moves further to the peripheral blood streams resulting sepsis or viremia. The virus further targets the organs which express ACE-2 such as lungs, heart, renal, gastrointestinal tract. Some studies shown that onset of infection the WBCs count was found to be normal or slightly low leading to lymphopenia i.e., infection may affect antibody production in the patient. By the time of 3 weeks the crucial period starts either it leads to recovery or death of the patient. The inflammatory factors associated with disease such as IL-6 are also reported to be increased contributing an aggravation of the disease 7-14 days after infection. It has been also reported that in some infected patients exuberant inflammatory response found which is similar to cytokine release syndrome which may leads to critical and fatal illness. It is accompted that the clinical phase includes viremia, acute pneumonia and recovery. If the patient is not immunocompromised the disease can be recovered in acute phase as when the immunity is low the WBCs gets reduced with increase in

inflammatory cytokines. It has been also observed that in severe patients development of disseminated intravascular coagulation possibly due to high rate inflammation in vascular wall. [12] [13] [14] [16]

The clinical manifestations and symptoms are quite similar to Rhinoviruses (Common cold) identified by nasal discharge and malaise. The incubation period of coronavirus is of 14 to 27 days, it infects upper respiratory tract majorly generating pneumonia, sever respiratory disease to lung failure. The common clinical features of Coronavirus-2 are Fever, Fatigue, Dry Cough, Anorexia, Myalgia, Dyspnea, Anosmia/ Dysensia (loss of smell and taste), Gastrointestinal pain, Nausea, Diarrhea. Because of the infection alveoli gets filled with fluid and the oxygen-carbon dioxide exchange becomes difficult with cough and breathing problems. The state of sever pneumonia or ARDS (acute respiratory distress syndrome) or lung failure takes place. The patients kept on ventilatory support systems due to ARDS. The death rate is higher among elderly people. [7] [15] [16]

Epidemiology and Transmission:

According to the study the very first coronavirus (MERS-CoV) were transmitted from Camels, SARS CoV from Civet Cat and the reservoir for the novel corona virus (SARS-CoV-2/ COVID-19) is said to be transferred from pangolin but it is not confirmed by any study yet.

Bats are said to be the natural hosts while pangolin and snakes are said to be intermediate hosts. The very first study had shown that it might spread through snakes but later it was proven that no such evidence that snakes behaves as intermediate hosts. In some studies the sequencing shown that there is 96% similarity between COVID-19 and the corona virus found in bat, so it is said that bats the possible source of spread. But recent studies done via macro-genomic sequencing, molecular biological detection have shown that the strain isolated form Pangolin and the strain isolated form human are 99% similar proving that pangolin is the potential intermediate host of SARS-COV2 through the results are not fully elucidate the potential of natural/ intermediate host of SARS-COV2. At present the potential source of infection and mode of transmission infected patients only. It's still not clear that the period of incubation inside the patient is also behaves as a transmission phase of this virus. [15] [16] [17]

According to the proven epidemiological studies, there are majorly 3 conditions for the wide spread of the virus: 1. **The source of infection, route of transmission, and susceptibility.;**

2. **There is no exception for SARS COV.** [16] [17]

Route of Transmission

Close contact is the most common way of transmission. Apart from that aerosol, surface contact can also be reasons of transmission. Genetic samples were detected in different tissues of gastrointestinal tract, conjunctival secretions, etc. The reported latency period of SARS-CoV is 14 days. If we look from median point of view COVID-19 have a shorter incubation period than that of SARS and MERS i.e., 24 days maximum period which may increase the risk of transmission. It has also been proven the progression of disease is faster in old age people than that of younger ones. [17] [18]

Infectivity Period

Transmission of the virus occurs prior to the development of symptoms and throughout the course of illness. The viral RNA levels are higher on the time of setting symptoms, so it shows that patients are more tend to spread infection in earlier state of infection than that in later stages. The viral shedding depends upon the severity of illness. In a study the median duration of viral particle shedding from the upper respiratory tract was of 24 days minimum and maximum of 42 days. Risk of transmission grows when proper sanitation and personal protective equipment are not in use. The chances of spread of infection is higher in case of gathering, face to face communication and conversations, contaminated food consumption, gestures exchanged with any infected person, coming in contact with any contaminated surface, etc. [18]

Diagnosis:

The general diagnosis of a suspect of CoVid-19 is to observe the symptoms such as high fever, cold, cough, sneezing, sore throat. However some of the cases reported not to show such symptoms prominently i. e., asymptomatic condition so, the molecular level tests are the best way to detect a positive case. There are 41 regulatory authorized diagnostic tests available till date. The diagnostic test types or scientific technology used for detection are PCR, next gen sequencing (NGS) and isothermal amplification. According to the current information viral nucleic acid detection is the most standard non-invasive diagnosis available for Covid-19. The detection through these methods are highly specific and less

sensitive, so the false negative are prominent and the time for testing can be longer as well. A report says that for the rapid detection of the virus, Zhang F of MIT University under Sherlock Technologies developed a test paper which can detect the presence of virus in one hour. It is under clinical verification. RT PCR is the most prominent method for detection in which the nasopharyngeal secretions are used to detect RNA extractions, RNA extracted from the deactivated virus particles is further purified and transcribed by RT PCR to synthesize complimentary DNA. A positive patient's sample cross the threshold line within 40 cycles. [19] [20]

A wide range of different tests are available in Serology. This should be indicated after onsetting of symptoms in second week probably with definite specificity and variable sensitivity. The serological tests required validation of experts as well. The lab tests for CoV-2 are complete blood count, D-dimer, lactic dehydrogenase (LDH), clotting tests, C-reactive protein (CRP), ferritin, and procalcitonin. All of these tests can identify the risk of disease with severity, thromboembolic complications, myocardial damage, and/or worse prognosis. Imaging tests such as CT scan is highly recommended to diagnose, especially when there are clinical symptoms but other tests showing negative results. [63]

Variants of Concern (VOC):

Researches have shown that this virus is mutating very fast. Multiple variants of CoV-2 are circulating globally. There are more than 70 new strains reported in which 3 are declared as variants of concern (VOC). On the basis of genome sequencing data of different samples collected from different states of the country, more than 700 cases were reported affected with the new strains.

New variants recently reported in India are **B.1.1.7** (reported in US in December 2020, initially detected in UK in September 2020), **B.1.351** (earlier reported in US at end of January 2021, initially detected in South Africa), **P.1** (earlier detected in US in January 2021). There are two more variants **E484Q** and **L452** were also found in some parts of India. [62]

Reasons of mutation:

RNA viruses are sensitive towards mutation. It changes gradually according to the geographic separations. The very first mutant B.1.1.7 was reported in UK in September 2020 responsible for 60% of new CoVid cases. It is prominent as a mutant in many other countries including India. This variant is more contagious and more lethal. This virus is

affecting the younger and the children both. Studies say if it will circulate more there are chances of further mutations which can turn this virus into more lethal and contagious and it's worrisome that similar changes are arising in the spike protein of the virus independently some mutation results in no change but some mutation alters the behaviour of the virus which results in different spike proteins and different key areas with changed attributes.

According to different studies, any mutation occurs at amino acid residues from 319 to 541, especially between 438-506 may significantly impact the infectiousness, transmissibility, severity, and its immunity evading potential. [62]

Current Treatment and Ongoing Research:

During the outbreak of this pandemic in 2019 and 2020 there was no clinically proven and directly effective antiviral therapy available for SARS-CoV 2 but with the blessing of science and the hard work of scientists we are able to fight back this pandemic viral disease.

Vaccine Research:

Vaccine researches are still in process. Researchers are working designing vaccine by using DNA, RNA, inactivated virus particle, live attenuated virus, non-replicative virus, protein subunits, replicating viral vectors, viruses like particle (VLP). There are more than 50 vaccines under development or in pre-clinical and clinical trials. [21] [22]

There are many vaccines which are already out for clinical trials and got approved by the health ministries of different governing bodies. The very first vaccine dosed a human was in USA named as 'mRNA-1273' produced by Moderna Company which was designed from synthetic mRNA to induce an immune response to produce antibodies against SARS-CoV-2. The other vaccine being developed in China namely Ad_{s-n}CoV by CanSino Bio with non-replicating viral vectors to deliver antigens to express the SARS-CoV-2 spike protein. The third vaccine is proposed in UK by the scientists of University of Oxford which was also developed from non-replicating viral vector to deliver RNA into cells. China proposed another vaccine namely LV-SMENNP-DC through scientists of Shenzhen Geno-Immune Medical Institute. This vaccine uses a lentiviral vector to deliver CoVid-19 minigenes to modify dendritic cells and activate T-cells. Another vaccine was tested by a research group in Netherlands namely BCG vaccine repurposing

to fight against CoV-2, this same vaccine was proposed in Australia as well by Murdoch Children's Research Institute for CoVid-19 patients. All of these vaccines were mostly used in Phase I, II and III. [23] [24]

Recently one vaccine has approved by the Ministry of Health of the Russia Federation in 2020. This vaccine 'Sputnik V' formerly known as Gam-COVID-Vac is developed by Gamaleya Research Institute in Moscow. Many experts have raised concern about its safety and efficacy. [25] This vaccine is made up of genetically modified cold virus which will deliver small fragment of coronavirus to human body in terms of priming the immune system to fight with the coronavirus. The jab uses two different version of vaccine using different vectors both of the vectors target the spike protein. The idea behind is to use two different formulas which will boost the immune system even more which may provide long lasting protection. It is 92% effective against CoV-2. This vaccine is under approval for vaccination drive in India but its efficacy is limited against the new variants of this virus.

In India there are two vaccines approved by health ministry in 2021 Covaxin and Covishield which are said to be highly effective.

Covaxin is an inactivated vaccine which is developed by the "Bharat Biotech Ltd." an Indian pharmaceutical company from a strain of coronavirus isolated by the National Institute of Virology. This vaccine uses inactivated virus (killed virus) which is recognized by the immune system and leads to the production of antibodies. Covaxin is given in two doses four weeks apart.

The Oxford AstraZeneca (Covishield) vaccine is designed by the "Serum Institute of India" (world's largest vaccine manufacturer). This vaccine is made up of a weakened version of a virus causing common cold (adenovirus). The jab is administrated between 4 to 12 weeks apart which is designed by "Pfizer BioNTech".

There are other vaccines as well which are under clinical trials and waiting for further approval ZyCoV-Di by "Zydus-Cadila", HGCO19 by Genova in collaboration with Seattle based private pharma company HDT Biotech Corp., NovaVax. [61]

The below table is showing the comparative performance of the available vaccines in India against CoV-2 and its new variants: (Source: Dr Vipin Vashishtha)

S.No.	Vaccine	Original' (symptomatic)	B.1.1.7 (symptomatic)	B.1.351 (symptomatic)	P.1 (symptomatic)
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1.	AstraZeneca (Covishield)	81.50%	70.40%	10.40%	NA
2.	Novavax	89%	85.60%	49-60%	NA
3.	J&J (Janssen)	72%	NA	57-64%	68%
4.	Pfizer	95%	Neutralisation decreased 2x	Neutralisation decreased 6.5x	Neutralisation decreased 6.7x
5.	Moderna	94.10%	Neutralisation decreased 1.8x	Neutralisation decreased 8.5x	Neutralisation decreased 4.5x

Drugs and Therapies:

Drugs and therapies in use to combat CoVid-19 around the world are selective namely Arbidol, Cermostatmesylate, Hydroxy chloroquine, Lopinavir, Darunavir, Ribavirin, Remdesivir, Flavipiravir, Blood thinners and Plasma therapy. [26]

Chloroquine and Hydroxychloroquine

This drug is commonly used for the malaria treatment and chronic inflammatory diseases. Studies reported that it blocks the entry of the virus into cells. It inhibits the glycosylation of host receptors, proteolytic processing and acidification of the endosomes. It was in use for the treatment of CoV-2 widely, it inhibits the virus with half maximal effective concentration [EC₅₀] in the low micro molar range. Dosing has consisted of 500mg orally once or twice daily but according to some studies dosing recommendation is 400mg orally once a day or 200mg orally twice a day. Common side effects such as abdominal cramps, anorexia, diarrhea, nausea and vomiting are also reported. For this drug there are several studies and clinical trials have been done but still there is no high quality data

published or reported about the efficacy of this drug in terms of treating CoV-2 effectively.[27] [28] [29] [30] [31] [32] [33] [34] [35]

Ribavirin

It is an analogue to guanine. According to studies, it's highly effective against CoV-2 as it inhibits the RNA dependent RNA polymerase. But it is required to be dosed in high concentrations for invitro activity against CoV-2 to inhibit viral replication. The dosage is nearly 1.2 to 2.4 grams orally in every 8 hours with combination of therapy. Some studies suggests it can also be given intravenously or external administrations but in combination with interferons. This drug is having a limited value of treatment because it causes sever dosage dependent hematological toxicity resulting in hemolytic anemia. [36] [37] [38] [39] [40]

Antiretrovirals (Lopinavir/Ritonavir/Darunavir)

These drugs are approved by US Food and Drug Administration (FDA) approved oral combination for the treatment of HIV. There is no published data found for effectiveness towards coronavirus but in some articles it had demonstrated invitro activity against some other CoVs via inhibiting 3-chymotrypsin like protease. In some clinical reports it is found to be effective on few patients who received the drug therapy within 12-14 days. The recommended dosing for this drug is 400mg/100mg twice daily up to 12-14 days. Similarly other antiretroviral drugs can also be effective via enzyme inhibition mechanism but there is no published data found. [41] [42] [43] [44] [45]

Umifenovir (Arbidol)

According to many different studies this drug is one of the promising repurposed antiviral agent with a unique mechanism of action against the virus particles. It targets the S-protein/ ACE2 interaction and inhibiting the membrane fusion of viral envelope. The suggestive dose for this drug is 200mg orally in 8 hours. There is a limited clinical data available of using this drug as a potent antiviral agent in terms of treatment of CoV-2. [46] [47] [48] [55]

Favipiravir

It was previously known as T-705. It is known as prodrug of a purine nucleotide (Favipiravir ribofuranosyl-5'-triphosphate). This antiviral agent inhibits the RNA polymerase of the virus and halts the whole viral replication mechanism. Previous studies have shown its effectiveness in treatment of viral diseases such as Influenza and Ebola.

The loading dose is of 2400mg to 3000mg every 12 hours in 2 times followed by maintenance dosage of 1200mg to 1800mg in every 12 hours. There is a limited clinical data has been reported for the use of this drug in the treatment of CoV-2. [49] [50] [51] [52] [53] [54] [55]

Remdesivir

It is known as GS-573U (monophosphate prodrug). It is highly effective towards RNA viruses (Flaviviruses, Coronaviruses). This drug was very effective during the Ebola outbreak. Due to its broad spectrum potential it is a promising drug in treatment of CoV-2. Many studies have been shown that this drug prevents lung hemorrhage and reduce viral titers in lungs comparatively to other drugs. This drug acts as an analogue for Adenosine Tri Phosphate (ATP) and competes naturally with ATP substrate for incorporation into nascent RNA chain of CoV-2 RNA dependent RNA polymerase, resulting in the chain termination, halting the viral replication process. The loading dose of this drug is 200mg to 100mg IV infused over 30-120 minutes with or without require mechanical ventilation for 1-10 days. [56] [57] [58] [59]

Blood Thinners

A research reported in Journal of the American College of Cardiology some patients were tested and treated with blood clot preventers which decreased the death rate by 29%. But the study was not randomized so it cannot prove that blood thinners are directly effective on CoV-2.

Plasma Therapy

According to some studies done in China severely ill CoVid-19 patients were treated with convalescent plasma (CP). The patients had shown significant improvement with in 3 days with raised antibodies titer and reduced viral load. This therapy involved taking plasma from the cured CoVid-19 patients and injecting it directly to the blood stream of the suffering patient. It is reportedly highly effective therapy for the treatment of CoV-2.

Other Therapies

Researchers trying to find different better ways to treat this sever disease but in absence of proven therapy there are some adjunctive therapies used namely Corticosteroids therapy, anticytokine or immunomodulatory agents, and immunoglobulin therapy.

Nanotechnology a future prospect:

Nanotechnology can be used to develop nano-vaccines which can be very helpful in the treatment of CoVid-19. According to a recent study an idea is proposed to design a nano-vaccine using viral proteins through which immunogenic peptides can be presented both on surface or encapsulated form. It will consist of multiple epitopes which can be both presented as adsorbed or encapsulated and can be studied both invitro and in vivo to check the immune responses raised by the viral epitopes. Nano-vaccines may be non-infectious as they cannot revert to virulent state and there is a very less risk of allergy.

Prevention: [2]

The novel corona virus is a great problem of this year and till today there are very less clinical approved treatment available for this infectious disease and the prevention is also very crucial at this stage. As different properties of this virus makes the prevention difficult and less effective as at each and every stage of this disease the infected person is spreading the virus whether its initial stage or its clinical recovery stage. The effective prevention of this infectious disease is only can be done by following the proper sanitization guidelines provided by the World Health Organization.

Isolation of the infected person is mandatory. Suspects with mild symptoms should be kept under surveillance of health worker. Proper ventilation should be provided to the infected person. Patients should be asked to cover their face with a protective shield/ cover. Care takers should avoid close contact. Health care workers, care takers of infected person should cover themselves with PPE suit or recommended facial mask and shield. Proper sanitization should be done nearby patients. After coming in contact with any of suspect or surface area hand should be washed and sanitized properly before touching mouth, nose or eyes.

Family members and relatives of the suspect and infected person should go through suggested tests and available preventive measures. Avoid large gatherings, unnecessary travelling to infected/ contaminated area or city. Hygiene practices should be followed properly for coughing, sneezing and sanitization of areas.

All of health workers, hospital staff, other officials should keep themselves updated about any kind of pandemic disease to prevent spillover.

Conclusion:

This review enlighten about the general information about the novel corona virus, how it become pandemic and the available mediums of treatment and preventive measures.

Covid-19 has challenged the world economic, medical and public health infrastructure. This pandemic had shown that how a virus can turn the tables and bring crisis in the global healthcare sector. There are several ongoing researches to find a treatment but in past year there was no effective clinically assured and approved treatment available which lead to global crisis. The vaccines and specific drugs are available in the market which is approved to provide required protection. But such viruses are threat to life because of their capability to mutate. So, it is recommended to be aware about infectious disease, their symptoms, treatment and preventive measures to avoid such pandemics in future.

References:

1. Huang C., Wang Y., Li X., Ren L., Zhao J., hu Y., et al. (2020). Clinical features of patients infected with 2019 novel corona virus in Wuhan, China, Lancet (London, England), 395, 497-506.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19- 11 March 2020. 2020. Available Online: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>(Accessed on March 12 2020).
3. Liu Y., Gayle A., A., Wilder-Smith A., Rocklov J. (2020) The reproductive number of COVID-19 is higher compared to SARS coronavirus. Journal of Travel Medicine.
4. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., et al. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet.
5. Organization W., H. Coronavirus disease 2019(COVID-19) Situation Report-40. (2020).
6. Chan J.,F., To K., K., Tse H., Jin D., Y., Yuen K., Y. (2013) Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiology. 21, 544-55.

7. Jawetz, M., & Adelberg's. (2004) Medical Microbiology. (23rd ed.). New York, N.Y.: Lange Medical Books/McGraw-Hill, Medical Pub. Division.
8. Levinson, W. (2020) Review of medical microbiology and immunology. (13th ed.). New York, N.Y.: Lange Medical Books/McGraw-Hill, Medical Pub. Division.
9. Ananthanarayan R., Paniker C., K., J. (2005). Textbook of Microbiology. (7th ed.). Himayatnagar, Hyderabad: Orient Longman.
10. Hoffmann M., Kleine-Weber H., Krüger N., Müller M., Drosten C., Pöhlmann S. (2020). The novelcoronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellularprotease TMPRSS2 for entry into target cells. *bioRxiv*. 2020.01.31.929042.
11. Richman D., D., Whitley R., J., Hayden F., G. (2016) Clinical Virology. (4th ed.). Washington: ASM Press.
12. Chen Y., Liu Q., Guo D. (2020) Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of Medicine Virology*. 92, 418-423. 10.1002/jmv.25681
13. Fehr A., R., Perlman S. (2015) Coronaviruses: an overview of their replication and pathogenesis .*Methods of Molecular Biology*. 1282, 1-23. 10.1007/978-1-4939-2438-7_1
14. Chan-Yeung M., Xu R., H. (2003) SARS: epidemiology. *Respirology*. 8, S9–14.
15. Chen N., Zhou M., Dong X., et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 395, 507–13.
16. Lu R., Zhao X., Li J., et al. (2020). Genomic characterization and epidemiology of 2019 novelcoronavirus: implications for virus origins and receptor binding. *Lancet*. 2020, 395:565-574. 2020 Hassan et al. *Cureus* 12(3): e7355. DOI 10.7759/cureus.7355 6 of 710.1016/S0140-6736(20)30251-8
17. Rothe C., Schunk M., Sothmann P., et al. (2020). Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *Journal of Medicine*. <https://doi.org/10.1056/NEJMc2001468>
18. Cheng Z., J., Shan J. (2020). 2019 novel coronavirus: where we are and whatwe know. *Infection*. 1–9. <https://doi.org/10.1007/s15010-020-01401-y>

19. Jin Y., H, Cai L, Cheng ZS, et. al. A rapid advice guideline for the diagnosis and treatment of 2019 novel corona virus [2019-nCoV] infected pneumonia [standard version]. *Mil Med Res.* 2020;7:4.
20. Chen Z., M., Fu J., F., Shu Q., et al. (2020). Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World Journal of Pediatrics.* 1-7. <https://doi.org/10.1007/s12519-020-00345-5>.
21. Zou L., Ruan F., Huang M., et al. (2020). SARS-CoV-2 viral load in upperrespiratory specimens of infected patients. *New England Journal of Medicine.* <https://doi.org/10.1056/NEJMc2001737>
22. Kampf G., Todt D., Pfaender S., Steinmann E. (2020). Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidalagents. *Journal of Hospital Infection.* pii: S0195-6701(20)30046-3
23. Wang D., Hu B., Hu C., et al. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA.* <https://doi.org/10.1001/jama.2020.1585>.
24. Xu X.,W., Wu X., X., Jiang X., G., et al. (2020). Clinical findings in a group ofpatients infected with the 2019 novel coronavirus (SARS-Cov-2)outside of Wuhan, China: retrospective case series. *BMJ.* 368:m606.
25. <https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker>
26. Savarino A., Boelaert J., R., Cassone A., Majori G., Cauda R. (2003). Effects of chloroquine on viral infections: an old drug against today's diseases?. *Lancet Infection Disease.* 3(11), 722-727. doi:10.1016/S1473-3099(03)00806-5
27. Al-Bari M., A., A. (2017). Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. *Pharmacology Research & Perspectives.* 5(1), e00293. doi:10.1002/prp2.293
28. Zhou D., Dai S., M., Tong Q. (2020). COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy.* dkaa114. doi:101093/jac/dkaa114
29. Devaux C., A., Rolain J., M., Colson P., Raoult D. (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-

19? International Journal of Antimicrobial Agents. doi:10.1016/j.ijantimicag.2020.105938

30. Colson P., Rolain J., M., Lagier J., C., Brouqui P., Raoult D. (2020). Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. International Journal of Antimicrobial Agents. doi:10.1016/j.ijantimicag.2020.105932

31. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novelcoronavirus pneumonia. Accessed March 18, 2020. <https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf>

32. Chloroquine [database online]. Hudson, OH: Lexicomp Inc; 2016. Accessed March 17, 2020. <http://online.lexi.com>

33. Aralen (chloroquine phosphate) [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2008. Accessed March 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/006002s045lbl.pdf

34. Yao X., Ye F., Zhang M., et al. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2.

35. Stockman L., J., Bellamy R., Garner P. (2006). SARS: systematic review of treatment effects. PLoS Medicine 3(9), e343. doi:10.1371/journal.pmed.0030343

36. Morra M., E., Van Thanh L., Kamel M., G., et al. (2018). Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. Reviews in Medical Virology. 28, (3):e1977. doi:10.1002/rmv.1977

37. ClinicalTrials.gov. Accessed March 18, 2020. <https://clinicaltrials.gov/>

38. Wu C., Chen X., Cai Y., et al. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirusdisease 2019 pneumonia in Wuhan, China. JAMA International Medicine.

39. Foolad F., Aitken S., L., Shigle T., L., et al. (2019). Oral versus aerosolized ribavirin for the treatment of respiratory syncytial virus infections in hematopoietic cell transplant recipients. Clinical Infectious Diseases. 68(10), 1641-1649. doi:10.1093/cid/ciy760

40. Arabi Y., M., Shalhoub S., Mandourah Y., et al. (2019). Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clinical Infectious Disease*. doi:10.1093/cid/ciz544
41. Chu C., M., Cheng V., C., Hung I., F., et al. (2004). HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. doi:10.1136/thorax.2003.012658
42. de Wilde A., H., Jochmans D., Posthuma C., C., et al. (2014). Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrobial Agents Chemotherapy*. 58(8), 4875-4884. doi:10.1128/AAC.03011-14
43. Cao B., Wang Y., Wen D., et al. (2020). A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *New England Journal of Medicine*. doi:10.1056/NEJMoa2001282
44. Lopinavir/ritonavir [database online]. Hudson (OH): Lexicomp Inc; 2016. Accessed March 17, 2020. <http://online.lexi.com>
45. Kaletra (Lopinavir and ritonavir) [package insert]. North Chicago, IL: Abbvie; 2019. Accessed March 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021226s048lbl.pdf
46. Kadam R., U., Wilson I., A. (2017). Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc Natl Acad Sci U S A*. 114(2), 206-214. doi:10.1073/pnas.1617020114
47. Khamitov R., A., Loginova S., Ia., Shchukina V., N., Borisevich S., V., Maksimov V., A., Shuster A., M. (2008). Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures [in Russian]. *Vopr Virusol*. 53(4), 9-13.
48. Wang Z., Yang B., Li Q., Wen L., Zhang R. (2020). Clinical Features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clinical Infectious Diseases*. doi:10.1093/cid/ciaa272
49. Furuta Y., Komeno T., Nakamura T. (2017). Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan Academy*,

Series B Physical and Biological Sciences. 93(7), 449-463.
doi:10.2183/pjab.93.027

50. Mentre F., Taburet A., M., Guedj J., et al. (2015). Dose regimen of favipiravir for Ebola virus disease. *Lancet Infectious Diseases*. 15(2), 150-151.
doi:10.1016/S1473-3099(14)71047-3

51. Sissoko D., Laouenan C., Folkesson E., et al. (2016). JIKI Study Group. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial a historically controlled, single-arm proof-of-concept trial in *PLoS Medicine* 13(4), e1002009. *PLoS Medicine*. 13(3), e1001967. doi:10.1371/journal.pmed.1001967

52. Shiraki K., Daikoku T. (2020). Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacology Therapeutics*. 107512.
doi:10.1016/j.pharmthera.2020.107512.

53. Chinello P., Petrosillo N., Pittalis S., Biava G., Ippolito G., Nicastri E. (2017). INMI Ebola Team. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. *PLoS Neglected Tropical Disease*. 11(12), e0006034.
doi:10.1371/journal.pntd.0006034

54. Kumagai Y., Murakawa Y., Hasunuma T., et al. (2015). Lack of effect of favipiravir, a novel antiviral agent, on QT interval in healthy Japanese adults. *International Journal of Clinical Pharmacology & Therapeutics*. 53(10), 866-874.
doi:10.5414/CP202388

55. Chen C., Huang J., Cheng Z., et al. (2020). Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. *medRxiv*.
doi:10.1101/2020.03.17.20037432

56. Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M., et al. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*. 10-0282.

57. Cascella M., Rajnik M., Cuomo A., Dulebohn S., C., Napoli R., D. (2020) Features, Evaluation and TreatmentCoronavirus (COVID-19). *StatPearls Publishing*, Treasure Island, FL.

58. Zhu N., Zhang D., Wang W., et al. (2020). China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China,

2019. New England Journal of Medicine. 382(8), 727-733. doi:10.1056/NEJMoa2001017

59. Hoffmann M., Kleine-Weber H., Schroeder S., et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. doi:10.1016/j.cell.2020.02.052.

60. <https://www.bbc.com/news/world-asia-india-55748124>

61. <https://science.thewire.in/the-sciences/are-the-new-variants-driving-indias-second-covid-19-wave/>

62. Cherian S. et al. (2021) Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv, <https://doi.org/10.1101/2021.04.22.440932>, <https://www.biorxiv.org/content/10.1101/2021.04.22.440932v1>

63. Goudouris E. S. (2021). Laboratory diagnosis of COVID-19. *Jornal de Pediatria*, 97(1), 7–12. <https://doi.org/10.1016/j.jped.2020.08.001>

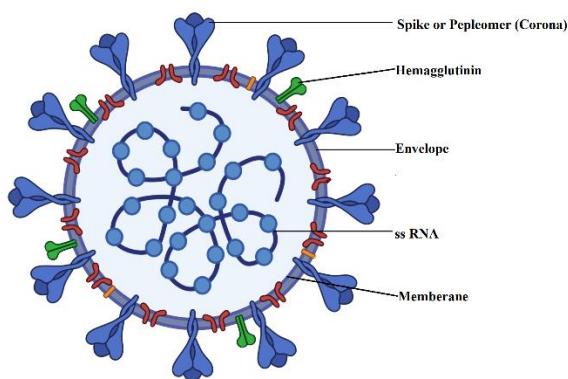


Figure 1: Diagram showing Corona virus particle having enveloped spherical structure representing a. ss positive sense RNA (N protein), b. envelope (E) protein, c. hemagglutinin (HE) protein, d. Membrane (M) protein, e. Spike (S) protein.

(a) (b) (c) (d) (e)

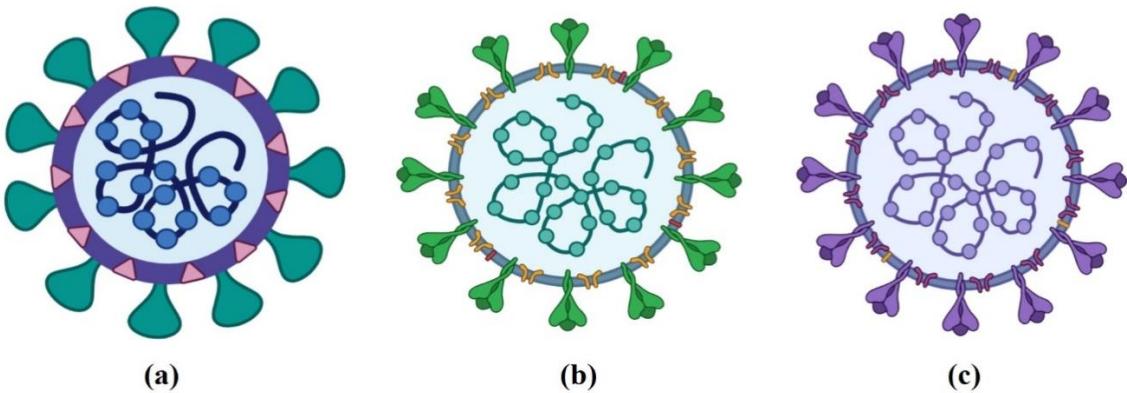


Figure 2: Diagram showing Different structures of Corona Virus Particles.

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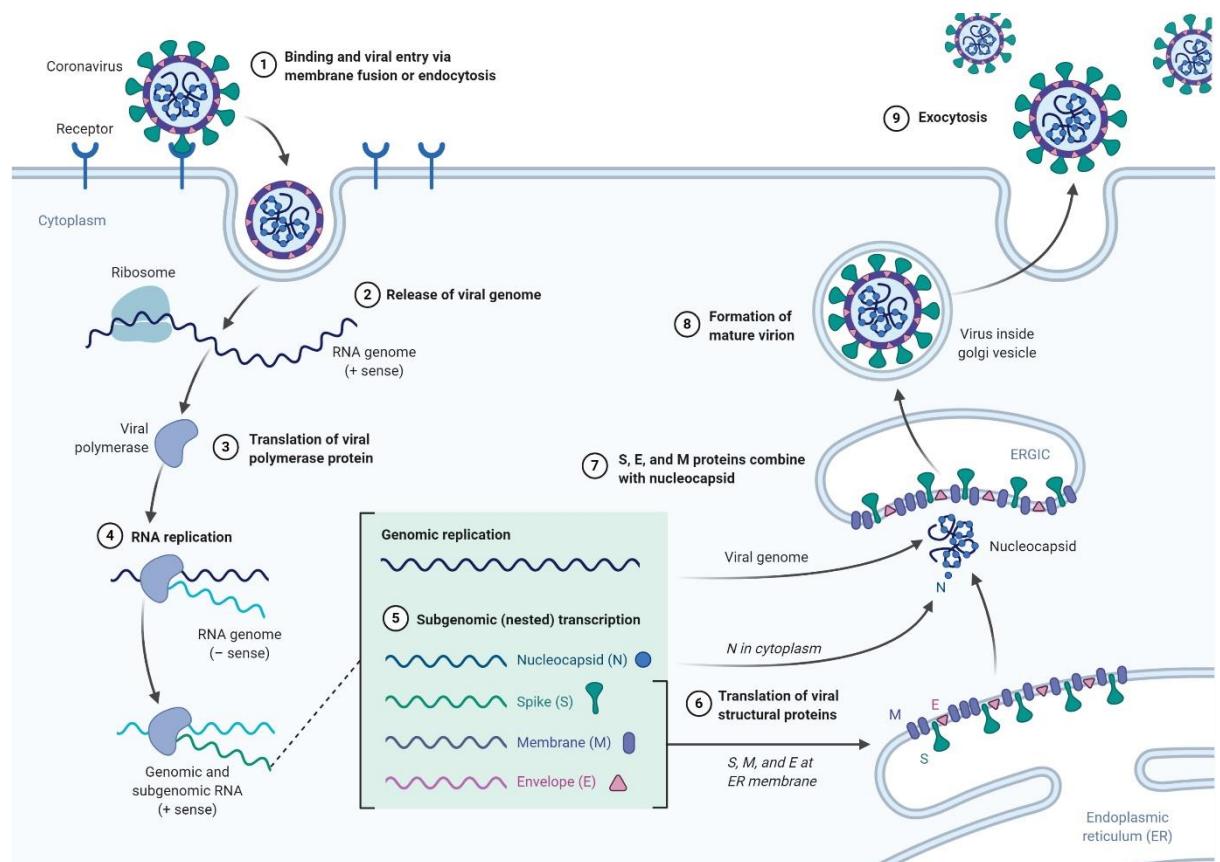


Figure 3: Diagrammatic representation of Replication of COVID-19. (created with biorender.com)

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Acute Respiratory Distress Syndrome (ARDS)
Alveolar Changes

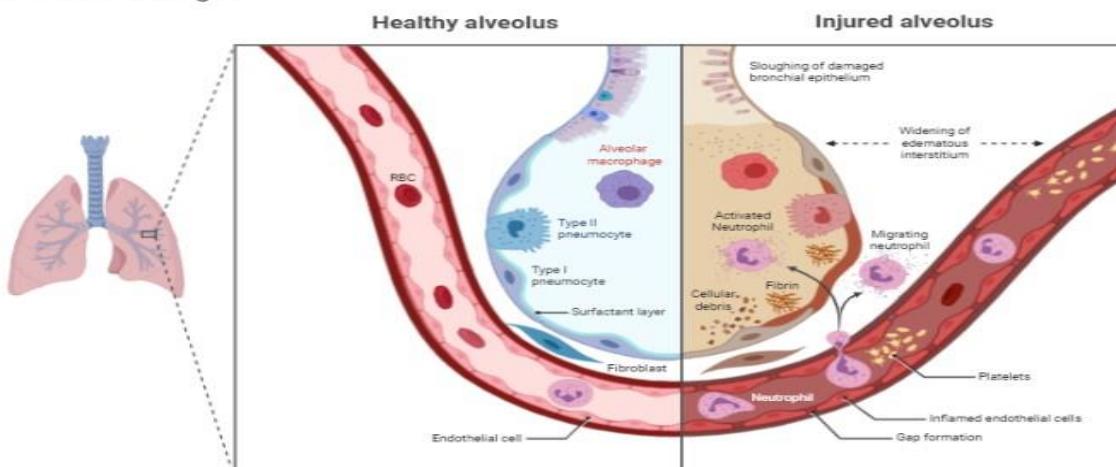


Figure 4: Diagrammatic representation of Acute Respiratory Distress Syndrome. (created with biorender.com)

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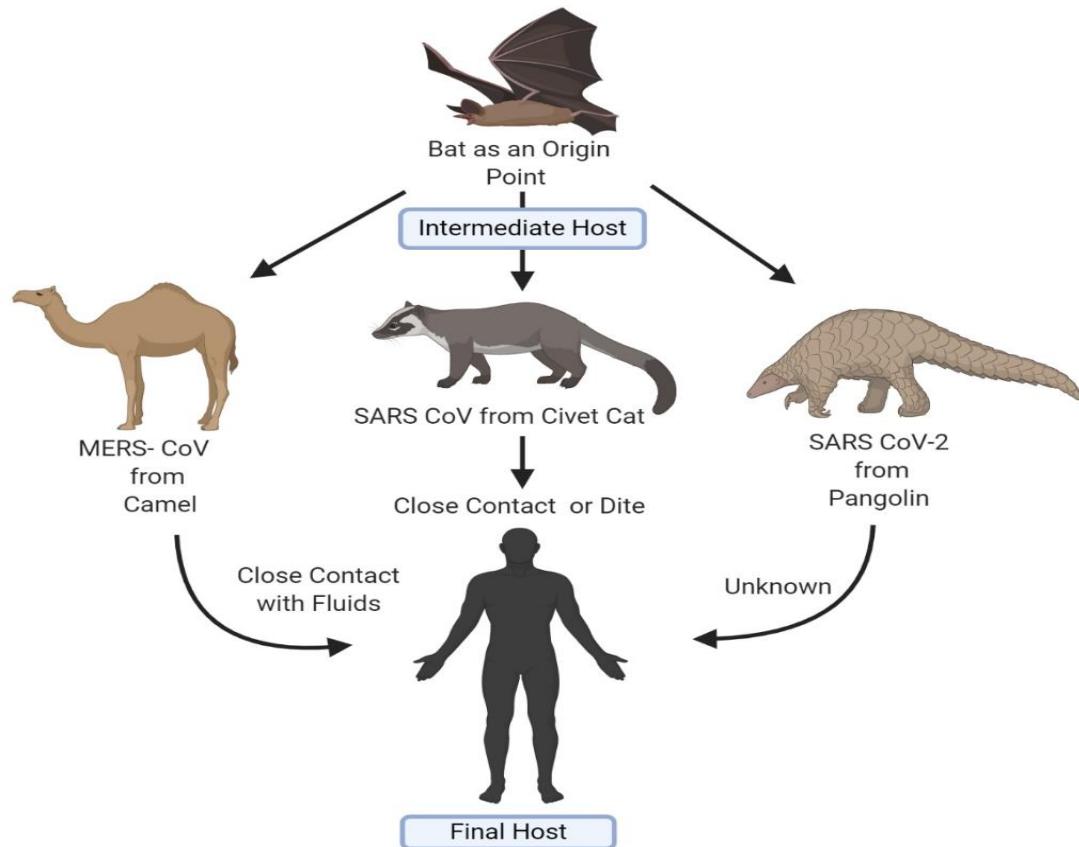


Figure: Diagram showing the possible transmission flow of COVID-19 virus.(created with biorender.com)

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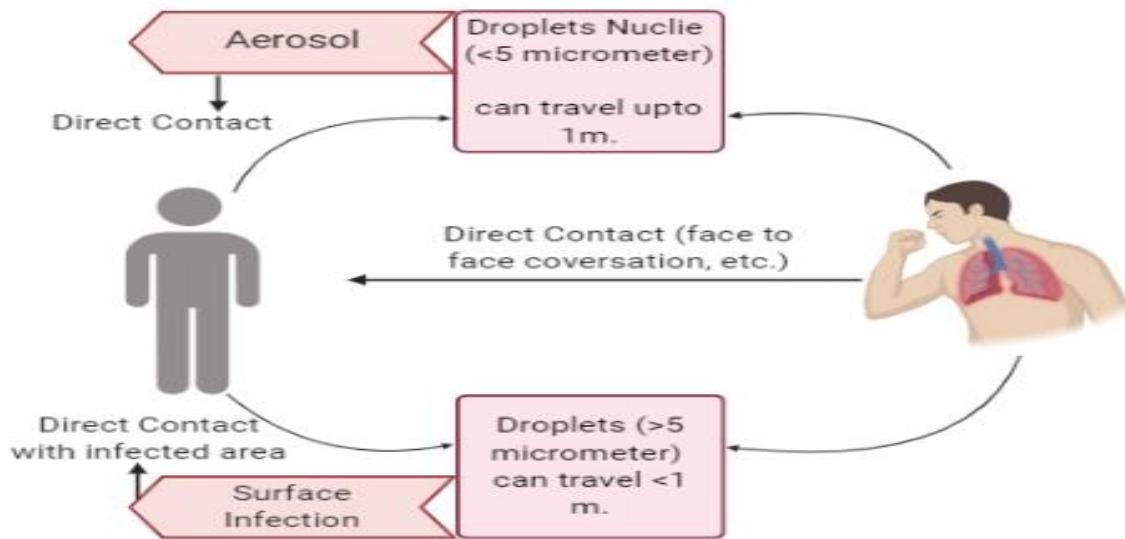


Figure: Diagram showing transmission of COVID-19 through an infected person both directly and indirectly. (created with biorender.com)

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COVID-19 Diagnostic Test through RT-PCR

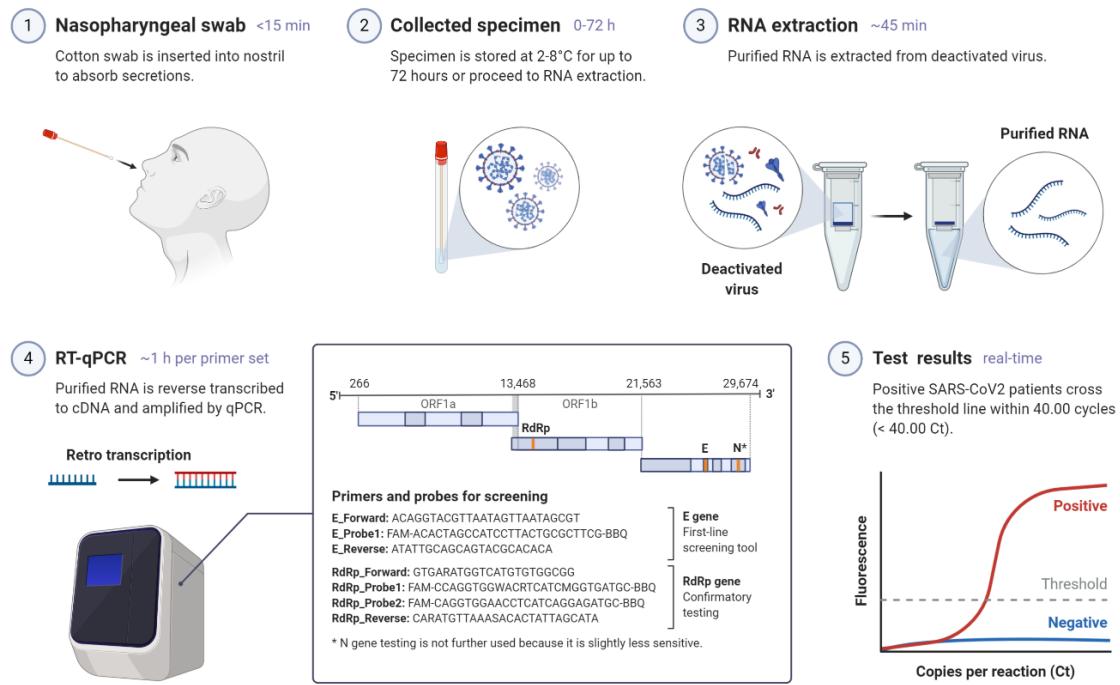


Figure: Diagram showing the diagnostic test for COVID-19 through RT PCR. (created with biorender.com)

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